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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,142	05/10/2001	Ilse Bartke	305T-900310US	6801

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	10

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,142	BARTKE ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *7-11,16 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12-15 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of the Claims

Claims 1-28 have been presented for examination.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-6, 12-15 and 17-25 in Paper No. 8, filed 03 October 2002 is acknowledged. The traversal is on the ground(s) that there is no burden. This is not found persuasive because burden was established by the separate classification, MPEP 803.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7-11, 16 and 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

N.B. Claim 6 was inadvertently included in Group II in the Office action of 26 September 2002 and has been regrouped with elected Group I.

Specification

The disclosure is objected to because of the following informalities: The proper continuity data does not appear to have been completed. The instant application is a CIP of 09/529,369 which depends from 08/833,959 which is not instantly claimed.

Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-6 and 12-15 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-6 and 12-15 of copending Application No. 09/529,369. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 12-15 and 17-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims 1-6 and 17-25 are drawn to a process for **preventing** demyelination of nerve fibers in the nervous system. Prevention is strong language and requires that the process, in

this case demyelination, **does not occur at all**. That is it means that demyelination does not occur to nerves that have been treated in the claimed manner and then challenged with a demyelinating insult. The examples have been carefully considered. There is no evidence of prevention, only a reduction in the degree of demyelination. Specifically, the specification discloses that there is a reduction in the extent of demyelination in marmoset brains following EAE induction. The examples clearly show that the number of lesions is **lower** in the NGF treated animal compared to the control animal which received the placebo of cytochrome C. This is not the same thing as prevention. The instant results are consistent with the interpretation that demyelination occurs, but not to the same extent as it would in the absence of NGF treatment.

In claims 12-15, the meaning of "preventing further demyelination" is not clear. Further how the data support such a claim is not clear. Neither this application nor prior applications 08/894,709 or 08/833,959 has support for "further preventing" demyelination. What is disclosed is that when demyelination was induced, there was a reduction in demyelination in the animals treated with NGF compared to untreated animals. That is, demyelination still occurs, it is neither protected against nor prevented. While this result may have clinical significance, it is not what is being claimed. There is a heavy burden on treatments that prevent particular disease states or conditions. There must be unequivocal evidence that the claimed method actually prevents the condition so that **it does not occur**. Given that prevention is a high standard and rarely met, a person of skill in the art considering the teachings of the instant disclosure would not expect that the claimed treatment method would prevent demyelination.

N.B. The claims in the instant application are rejected under 112, first paragraph as not enabled for "preventing". Using the specification to interpret the language of the claims, one

concludes that the claims are referring to a treatment of demyelination which is effective to reduce the extent of demyelination.

There is even a question if the claimed method can reduce demyelination in response to all known insults. Only a limited number of possible insults were considered and exemplified. It is not clear that these examples are suitably representative of the range of possible insults.

Absent clear evidence that the claimed process can be performed and that administration of NGF actually **prevents** demyelination, a person of skill in the art would have little reason to believe that NGF treatment functions in the manner claimed. Considerable testing without a reasonable likelihood of success would be required even at the design stages of the experiment to demonstrate that NGF treatment prevents demyelination.

Accordingly, the claims are not enabled for **preventing** demyelination and may not be commensurate in scope with all demyelinating insults.

Claims 1, 4-6, 12-13 and 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific fragments of NGF (2.5S and 7S), does not reasonably provide enablement for any "active" fragment or "analogue". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to any "active fragment" or "analogue" of NGF. However, aside from the specific fragments, C, no fragments have been identified that function in the claimed method. In fact the particular residues necessary for the structure and function of the "active fragments" have not been identified or disclosed. In other words, the residues of NGF

that may be deleted, added or substituted and still retain the desired activity have not been identified or disclosed. No general teaching of suitable analogues has been presented.

The disclosure alleges that active fragments can be used to prevent demyelination. However, no examples of active fragments were even tested for their ability to reduce demyelination let alone prevent demyelination. A person of ordinary skill in the art would have to test each every putative active fragment for the desired ability to reduce and prevent demyelination. Given the complexity and difficulty of performing the assay for activity, it would require undue experimentation to make and test all possible active fragments for the claimed activity. Those aspects of NGF that give rise to the allegedly newly discovered activity may not require the entire NGF molecule although the entire molecule is required to obtain the correct folding pattern of NGF for this activity. None of specifically recited fragments was tested for the claimed activity. The artisan would not know which fragments are likely on any structural or other basis. It would require an undue burden of experimentation to determine the residues that can be deleted, added or substituted to produce and active fragment and still retain the desired activity except for the deleted, except for 2.5S and 7S, or any general structural elements of an analogue. Accordingly, the claims are not commensurate in scope with the enabling disclosure with respect to active fragments or analogues.

Claims 1-6 and 17-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 17-25 seem incomplete because the therapy does not appear to be applied to a person in need of therapy. It is unclear how the need of the human for the claimed treatment is to be determined. That is, how does one know to prevent demyelination if the patient is not already suffering from the affliction? It is not like preventing disease transmission where an intervention can be used because demyelination is a degenerative disease and is not known to be transmissible, it is only detected.

Claims 3 and 25 recite "recombinant" which is vague and indefinite because it is not clear if the molecule is simply recombinantly produced or has been modified by recombinant techniques.

Claim 4 recites "further comprising" which lacks antecedent basis.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6 and 12-15 and 17-25 are provisionally rejected under 35 U.S.C. 102(b) as being anticipated by Diaz-Villoslada et al. (1996) or Diaz-Villoslada et al. (1997).

Diaz-Villoslada et al. (1996) or Diaz-Villoslada et al. (1997) disclose that EAE induced demyelination in marmoset brains can be reduced by animals which received a placebo of cytochrome C. It is said that NGF should be considered a therapeutic agent for MS (a human disease) and related disorders (which operate by inflammatory mechanisms). This is the same data as instantly presented and the title of the articles indicates that prevention is suggested. It is

noted that some of the authors of this paper are in common with the instant inventorship, there being more authors than instant inventors and that in prior application, 08/833,959 a Declaration was provided asserting that the other authors were not inventors. This rejection is provisional because 1) it is assumed that the benefit of priority to the earlier filed application will be perfected [making this a rejection under 102(a)] and 2) the Declaration will be transferred and thereby obviate the other authors.

Additional Prior Art

Althaus (WO 9303140) discloses that a pharmaceutical composition comprising NGF or an active fragment thereof can be used as a treatment for diseases in which demyelination of nerve fibers occurs (page 4, second paragraph). Some of these diseases included are set forth in the paragraph connecting pages 4-5. Specific active fragments include NGF-ß, NGF-2.5S, and NGF 7S (page 2, third full paragraph). The NGF-ß may be human recombinant. The compositions may further comprise a protease inhibitor, preferably aprotinin which is also known under the brand name of Trasylol® (page 3, last paragraph). Typical methods of administration are disclosed at page 5, first full paragraph, including intravenous. The amount to be administered is described in terms of ng/ml of blood over 48 hours by Althaus rather than the resulting microgram/kg body weight instantly claimed. These different dosage measurements are not clearly comparable. Claim 6 does not state how much is administered ("an amount sufficient"), but rather describes the resulting level in the treated patient. Thus, while Althaus provides the usual administrative dosage information, the therapeutic level is claimed instantly. Short of testing, there is no way to determine what dosage rate gives rise to a given level.

Clearance, tolerance and other factors are known in the art to effect the level of a therapeutic at any given dosage. These factors are also known to change during therapy, and hence the levels of a therapeutic are usually monitored. Since therapeutic levels are desired both in the instant application and in Althaus, it can be assumed that a "sufficient amount" of the composition will be administered to attain this level and therefore this is inherent in the process of treatment suggested by Althaus. Nevertheless, Althaus does not teach **preventing** demyelination, but rather shows a reduction in demyelination.

Unger et al. (1995) disclose that NGF (human recombinant) infusion (intracerebral or intraventricular) remediates lysolecithin induced demyelination and regeneration of nerve fibers in pig brains. The demyelination is said to be a model for demyelinating and secondary inflammatory diseases such as MS (a known human disease) and suggests the therapeutic potential of NGF.

Unger et al. (EP 731,108) discloses interval treatment of oligodendrocytes in multiple sclerosis with pharmaceutical compositions of human NGF-ß for the improved remyelination in nerve fibers compared to continuous treatment. It is not clear if "preventing further demyelination" of instant claims 12-15 means the same thing as increased remyelination in the demyelination model of Unger. If the answer is yes, then claims 12-15 are anticipated by Unger. If the answer is no, then Unger is no more enabling for preventing than the instant disclosure.

Bartke et al. (WO 9846254) is not prior art.

Unger et al. (US 6,268,340) is drawn to a method or regenerating oligodendrocytes that have been demyelinated. It does not appear that regeneration requires preventing further demyelination or preventing demyelination for action. If it does, then an obvious-type double patenting rejection is appropriate.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
January 13, 2003